

# Pattern Matching and Local Alignment for RNA Structures\*

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## Abstract

*The primary structure of a ribonucleic acid (RNA) molecule can be represented as a sequence of nucleotides (bases) over the alphabet  $\{A, C, G, U\}$ . The secondary or tertiary structure of an RNA is a set of base pairs which form bonds between  $A - U$  and  $G - C$ . For secondary structures, these bonds have been traditionally assumed to be one-to-one and non-crossing.*

*This paper considers pattern matching as well as local alignment between two RNA structures. For pattern matching, we present two algorithms, one for obtaining an exact match, the other for approximate match. We then present an algorithm for RNA local structural alignment.*

## 1 Introduction

Ribonucleic Acid (RNA) is an important molecule which performs a wide range of functions in biological systems. In particular, it is RNA (not DNA) that contains genetic information such as HIV and regulates the functions of such virus. RNA has recently become the center of much attention due to its catalytic properties, leading to an increasing interest in obtaining its structural information.

It is well known that secondary and tertiary structural features of RNAs are important in the molecular mechanisms involving their functions. The presumption is that, to a preserved function there corresponds a preserved molecular conformation and, therefore, a preserved secondary and tertiary structure. Hence the ability to compare RNA structures is useful [1, 3, 4, 5, 7, 14]. In many problems involving RNAs [2, 9], it is required to have an alignment between RNA structures in addition to a similarity measure [10]. In RNA secondary or tertiary structure, a bonded pair of bases (base pair) is usually

represented as an edge between the two complementary bases involved in the bond. It is assumed that any base participate in at most one such pair. For secondary structures, the edges of the bonded pairs are non-crossing.

In [14], a distance measure between two RNA structures is proposed. This measure takes into account the primary, the secondary and the tertiary information of RNA structures. This measure treats a base pair as a unit and does not allow it to match to two unpaired bases. In general this is a reasonable model since, in RNA structures, when one base of a pair changes, we usually find that its partner also changes so as to conserve that base pair. Computing edit distance for tertiary structures is proved to be NP-hard [14].

In [12], a model based on the one defined in [14] is proposed to take affine gap penalty into consideration. Experimental results show that the model in [12] performs better than that in [14].

In this paper, we consider a structural pattern matching problem and a local structural alignment problem.

In the first problem, specifically, given two RNA structures  $R_1$  and  $R_2$ , we want to find in  $R_2$  a pattern matched by  $R_1$ , with both exact match and approximate match. For exact match, we present a labelling device so that an RNA structural matching problem can be treated by existing fast string-matching algorithms. For approximate match, we present an algorithm based on the model defined in [12] with modifications to adapt to the RNA structural pattern matching problem.

In the second problem, specifically, given two RNA structures  $R_1$  and  $R_2$ , we want to find the most similar regions, one in each structure. We present an algorithm also based on the model defined in [12] with modifications to adapt to the RNA local structural alignment problem.

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## 2 RNA Structural Representation

Given an RNA structure  $R$ , we use  $R[i]$  to denote the  $i$ th base of an RNA structure  $R$ , and  $R[i \cdots j]$  the sequence of bases from  $R[i]$  to  $R[j]$ . We use  $|R|$  to denote the primary-sequence length of  $R$ . A set of structural elements for  $R$  may be represented by  $S(R)$ , where  $S(R) = U(R) \cup P(R)$ ,  $U(R) = \{i \mid R[i] \text{ is an unpaired base in } R\}$  and  $P(R) = \{(i, j) \mid i < j \text{ and } (R[i], R[j]) \text{ is a base pair in } R\}$ . For  $(i, j) \in P(R)$ ,  $i$  is called the 5' end, and  $j$  the 3' end. We assume that base pairs in  $R$  do not share participating bases. Formally, for any  $(i_1, j_1)$  and  $(i_2, j_2) \in P(R)$ ,  $j_1 \neq i_2$ ,  $i_1 \neq j_2$ , and  $i_1 = i_2$  if and only if  $j_1 = j_2$ . We define  $p(R[i])$  as

$$p(R[i]) = \begin{cases} i & \text{if } R[i] \in U(R), \\ j & \text{if } (R[i], R[j]) \text{ or } (R[j], R[i]) \in P(R). \end{cases}$$

By this definition,  $p(R[i])$  indicates if  $R[i]$  is an unpaired base (case 1) or a paired base (case 2) and with which base it pairs.

## 3 RNA Structural Alignment

Following the tradition in sequence comparison [8, 11], we define three edit operations on RNA structures: substitute, delete and insert. For a given RNA structure  $R$ , each operation can be applied to either an unpaired base or a base pair. To substitute a base pair is to replace one base pair with another. This means that at the sequence level, two bases may be changed at the same time. To delete a base pair is to remove the base pair. At the sequence level, this means to delete two bases at the same time. To insert a base pair is to insert a new base pair. At the sequence level, this means to insert two bases at the same time. There is no relabel operation to change a base pair to an unpaired base or vice versa.

We denote an edit operation by  $a \rightarrow b$ , where  $a$  and  $b$  are either  $\lambda$ , the null label, or labels of base pairs from  $\{A, C, G, U\} \times \{A, C, G, U\}$ , or unpaired bases from  $\{A, C, G, U\}$ .

We call  $a \rightarrow b$  a substitute operation if  $a \neq \lambda$  and  $b \neq \lambda$ ; a delete operation if  $a \neq \lambda$  and  $b = \lambda$ ; an insert operation if  $a = \lambda$  and  $b \neq \lambda$ . Let  $\Gamma$  be a similarity-scoring function that assigns to each edit operation  $a \rightarrow b$  a real number  $\Gamma(a \rightarrow b)$ . We constrain  $\Gamma$  to be a similarity metric.

Given two RNA structures  $R_1$  and  $R_2$ , we adopt the following sign convention.

$$\begin{aligned} \Gamma(R_1[i] \rightarrow R_2[j]) &\geq 0 \text{ if } R_1[i] = R_2[j], \\ \Gamma(R_1[i] \rightarrow \lambda) &\leq 0, \Gamma(\lambda \rightarrow R_2[j]) \leq 0, \\ \Gamma((R_1[i_1], R_1[i_2]) \rightarrow (R_2[j_1], R_2[j_2])) &\geq 0 \\ &\text{if } R_1[i_1] = R_2[j_1] \text{ and } R_1[i_2] = R_2[j_2], \\ \Gamma((R_1[i_1], R_1[i_2]) \rightarrow \lambda) &\leq 0, \\ \Gamma(\lambda \rightarrow (R_2[j_1], R_2[j_2])) &\leq 0. \end{aligned}$$

Given two RNA structures  $R_1$  and  $R_2$ , a structural alignment of  $R_1$  and  $R_2$  is represented by  $(R'_1, R'_2)$  satisfying the following conditions.

1.  $R'_1$  is  $R_1$  with some new symbols  $'-'$ , denoting a space, inserted and  $R'_2$  is  $R_2$  with some new symbols  $'-'$  inserted such that  $|R'_1| = |R'_2|$ .
2. If  $R'_1[i]$  is an unpaired base in  $R'_1$ , then either  $R'_2[i]$  is an unpaired base in  $R'_2$  or  $R'_2[i] = '-'$ . If  $R'_2[i]$  is an unpaired base in  $R'_2$ , then either  $R'_1[i]$  is an unpaired base in  $R'_1$  or  $R'_1[i] = '-'$ .
3. If  $(R'_1[i], R'_1[j])$  is a base pair in  $R'_1$ , then either  $(R'_2[i], R'_2[j])$  is a base pair in  $R'_2$  or  $R'_2[i] = R'_2[j] = '-'$ . If  $(R'_2[i], R'_2[j])$  is a base pair in  $R'_2$ , then either  $(R'_1[i], R'_1[j])$  is a base pair in  $R'_1$  or  $R'_1[i] = R'_1[j] = '-'$ .
4. If  $(R'_1[i], R'_1[j])$  and  $(R'_1[k], R'_1[l])$  are base pairs in  $R'_1$  and  $(R'_2[i], R'_2[j])$  and  $(R'_2[k], R'_2[l])$  are base pairs in  $R'_2$ , then  $(R'_1[i], R'_1[j])$  and  $(R'_1[k], R'_1[l])$  are non-crossing in  $R'_1$  and  $(R'_2[i], R'_2[j])$  and  $(R'_2[k], R'_2[l])$  are non-crossing in  $R'_2$ .

From the first three conditions, alignments preserve the order of unpaired bases and the topological relationship between base pairs. From the last condition, even though the input RNA structures may have crossing base pairs, the aligned base pairs are non-crossing.

A gap in an alignment  $(R'_1, R'_2)$  is a consecutive subsequences of  $'-'$  in either  $R'_1$  or  $R'_2$  with maximal length. Formally,  $[i \cdots j]$  is a gap in  $(R'_1, R'_2)$  if either  $R'_1[k] = '-'$  for  $i \leq k \leq j$ ,  $R'_1[i-1] \neq '-'$ , and  $R'_1[j+1] \neq '-'$ ; or  $R'_2[k] = '-'$  for  $i \leq k \leq j$ ,  $R'_2[i-1] \neq '-'$ , and  $R'_2[j+1] \neq '-'$ . For each gap in an alignment, in addition to the insertion/deletion penalty, we will assign a constant,  $G$ , where  $G < 0$ , as the gap penalty. This means that longer gaps are preferred since for a longer gap the additional penalty distributed to each base is relatively small.

Given an alignment  $(R'_1, R'_2)$ , we define single-base match  $SM$ , single-base deletion  $SD$ , single-base insertion  $SI$ , base-pair match  $PM$ , base-pair deletion  $PD$ , and base-pair insertion  $PI$ , as follows.

$$\begin{aligned}
SM &= \{i \mid R'_1[i] \text{ and } R'_2[i] \text{ are unpaired bases in } R_1 \text{ and } R_2\}. \\
SD &= \{i \mid R'_1[i] \text{ is an unpaired base in } R_1 \text{ and } R'_2[i] = \text{'-'}\}. \\
SI &= \{i \mid R'_2[i] \text{ is an unpaired base in } R_2 \text{ and } R'_1[i] = \text{'-'}\}. \\
PM &= \{(i, j) \mid (R'_1[i], R'_1[j]) \text{ and } (R'_2[i], R'_2[j]) \\
&\quad \text{are base pairs in } R_1 \text{ and } R_2\}. \\
PD &= \{(i, j) \mid (R'_1[i], R'_1[j]) \text{ is a base pair in } R_1 \text{ and } R'_2[i] = R'_2[j] = \text{'-'}\}. \\
PI &= \{(i, j) \mid (R'_2[i], R'_2[j]) \text{ is a base pair in } R_2 \text{ and } R'_1[i] = R'_1[j] = \text{'-'}\}.
\end{aligned}$$

The similarity score,  $\text{sim}((R'_1, R'_2))$ , of an alignment  $(R'_1, R'_2)$  is defined as follows, where  $N_g$  is the number of gaps in  $(R'_1, R'_2)$ .

$$\begin{aligned}
\text{sim}((R'_1, R'_2)) &= \sum_{i \in SM} \Gamma(R'_1[i] \rightarrow R'_2[i]) \\
&+ \sum_{i \in SD} \Gamma(R'_1[i] \rightarrow \lambda) + \sum_{i \in SI} \Gamma(\lambda \rightarrow R'_2[i]) \\
&+ \sum_{(i, j) \in PM} \Gamma((R'_1[i], R'_1[j]) \rightarrow (R'_2[i], R'_2[j])) \\
&+ \sum_{(i, j) \in PD} \Gamma((R'_1[i], R'_1[j]) \rightarrow \lambda) \\
&+ \sum_{(i, j) \in PI} \Gamma(\lambda \rightarrow (R'_2[i], R'_2[j])) + G \times N_g.
\end{aligned}$$

We are now in a position to consider three types of alignment between two RNA structures  $R_1$  and  $R_2$ . The common goal is to find the alignment with the maximum similarity.

1. Global alignment: Given two RNA structures  $R_1$  and  $R_2$ , find the alignment  $(R'_1, R'_2)$  with the maximum similarity alignment score,  $A_G(R_1, R_2) = \max_{(R'_1, R'_2)} \{\text{sim}((R'_1, R'_2))\}$ .
2. Local alignment: Given two RNA structures  $R_1[1 \dots m]$  and  $R_2[1 \dots n]$ , find the alignment  $(R'_1[i \dots j], R'_2[k \dots l])$  with the maximum similarity alignment score,  $A_L(R_1, R_2) = \max_{1 \leq i \leq j \leq m, 1 \leq k \leq l \leq n} \{\text{sim}((R'_1[i \dots j], R'_2[k \dots l]))\}$ .
3. Pattern matching: Given two RNA structures  $R_1[1 \dots m]$  and  $R_2[1 \dots n]$ , find the alignment  $(R'_1, R'_2[k \dots l])$  with the maximum similarity alignment score,  $A_M(R_1, R_2) = \max_{1 \leq k \leq l \leq n} \{\text{sim}((R'_1[1 \dots m], R'_2[k \dots l]))\}$ .

## 4 Exact Pattern Matching

In this section, we consider the exact RNA structural pattern matching problem.

**Exact RNA structural pattern matching:** Given a pattern RNA structure  $R_1$  and a text RNA structure  $R_2$  of lengths  $m$  and  $n$  respectively, determine all the positions where  $R_1$  occurs in  $R_2$ , that is, all positions  $i$  in  $R_2$  where

1. Primary sequences are identical:  $R_2[i \dots i+m-1] = R_1[1 \dots m]$ , and

2. Structures are identical: for any  $1 \leq j \leq m$ ,  $R_1[j]$  is an unpaired base if and only if  $R_2[i+j-1]$  is an unpaired base and for any  $1 \leq j < k \leq m$ ,  $(R_1[j], R_1[k])$  is a base pair if and only if  $(R_2[i+j-1], R_2[i+k-1])$  is a base pair.

**Lemma 4.1** *The exact RNA structural pattern matching can be solved in  $O(n+m)$  time.*

*Proof.* Given  $R_1$  and  $R_2$ , we first generate  $R'_1$  and  $R'_2$ . If  $R_1[i]$  is an unpaired base, then  $R'_1[i] = 0$  and if  $(R_1[i], R_1[j])$  is a base pair then  $R'_1[i] = j - i$  and  $R'_1[j] = i - j$ .  $R'_2$  is generated in the same manner.

Now we can first perform a standard string matching (KMP [6]) to find all positions where  $R_1$  occurs in  $R_2$  and then perform another standard string matching to find all positions where  $R'_1$  occurs in  $R'_2$ . These positions where  $R_1$  occurs in  $R_2$  and  $R'_1$  occurs in  $R'_2$  are the solution of this problem.  $\square$

## 5 Approximate Pattern Matching

In this section, we consider the approximate RNA structural pattern matching problem.

**Approximate RNA structural pattern matching:** Given two RNA structures  $R_1[1 \dots m]$  and  $R_2[1 \dots n]$ , find the best fit of  $R_1$  in  $R_2$ . That is, find the alignment  $(R'_1[1 \dots m], R'_2[k \dots l])$  which yields  $A_M(R_1, R_2) = \max_{1 \leq k \leq l \leq n} \{\text{sim}((R'_1[1 \dots m], R'_2[k \dots l]))\}$ .

This problem can be viewed as a variation of finding the optimal alignment between two RNA structures, in this case,  $R_1$  and a part of  $R_2$ . That is, which part in  $R_2$  gives the best alignment to  $R_1$ ? This problem resembles both global and local alignments in the sense that we have to match the entire  $R_1$  (global) to a part of  $R_2$  (local). What is presented here, therefore, is an adaptation of an algorithm by Wang and Zhang [12] for global alignment between two RNA structures taking affine gap penalty into consideration. We modify the algorithm in combination with a known algorithm for fitting one sequence into another [13] to yield an algorithm for approximate pattern matching with affine gap penalty between two RNA structures.

The algorithm is based on dynamic programming and uses a bottom-up procedure consisting of two phases. In the first phase, we compute global alignments between substructures in  $R_1$  and substructures in  $R_2$ . In the second phase, we take the two whole structures  $R_1$  and  $R_2$  and compute pattern matching.

## 5.1 Properties

In the original model [12], a distance measure is used. For the approximate algorithm in this paper, we convert the distance measure to the similarity measure.

Consider two RNA structures  $R_1$  and  $R_2$ . We use  $g$ , where  $g > 0$ , to denote the gap penalty. We use  $\gamma(i, j)$ , where  $1 \leq i \leq |R_1|$  and  $1 \leq j \leq |R_2|$ , to denote the similarity score for aligning two structural elements  $e_i \in S(R_1)$  and  $e_j \in S(R_2)$  (c.f., section 2). Note that  $\gamma(i, j)$  is positive if the two structural elements match, and negative otherwise. We use  $\delta(i, 0)$  and  $\delta(0, j)$ , where  $1 \leq i \leq |R_1|$  and  $1 \leq j \leq |R_2|$ , to denote the penalty of aligning  $R_1[i]$  and  $R_2[j]$ , respectively, to  $'-'$ . Note that  $\delta(i, 0)$  and  $\delta(0, j) > 0$ . We define  $\gamma$  and  $\delta$  in terms of  $\Gamma$  as follows.

$$\begin{aligned} \delta(i, 0) &= -\Gamma(R_1[i] \rightarrow \lambda) \\ &\quad \text{if } i = p(R_1[i]), \\ \delta(0, j) &= -\Gamma(\lambda \rightarrow R_2[j]) \\ &\quad \text{if } j = p(R_2[j]), \\ \gamma(i, j) &= \Gamma(R_1[i] \rightarrow R_2[j]) \\ &\quad \text{if } i = p(R_1[i]) \text{ and } j = p(R_2[j]), \\ \delta(i, 0) &= \delta(i', 0) = -\Gamma((R_1[i], R_1[i']) \rightarrow \lambda)/2 \\ &\quad \text{if } i = p(R_1[i']) < i' \leq |R_1|, \\ \delta(0, j) &= \delta(0, j') = -\Gamma(\lambda \rightarrow (R_2[j], R_2[j']))/2 \\ &\quad \text{if } j = p(R_2[j']) < j' \leq |R_2|, \\ \gamma(i, j) &= \Gamma((R_1[i'], R_1[i]) \rightarrow (R_2[j'], R_2[j])) \\ &\quad \text{if } 0 < i' = p(R_1[i]) < i \text{ and } 0 < j' = p(R_2[j]) < j. \end{aligned}$$

Consider the optimal-alignment score between  $R_1[i_1 \dots i_2]$  and  $R_2[j_1 \dots j_2]$ . We use  $A(i_1 \dots i_2, j_1 \dots j_2)$  to denote the optimal-alignment score between  $R_1[i_1 \dots i_2]$  and  $R_2[j_1 \dots j_2]$ ,  $D(i_1 \dots i_2, j_1 \dots j_2)$  the optimal-alignment score between  $R_1[i_1 \dots i_2]$  and  $R_2[j_1 \dots j_2]$  such that the alignment ends with  $R_1[i_2]$  aligned to  $'-'$ , and  $I(i_1 \dots i_2, j_1 \dots j_2)$  the optimal-alignment score between  $R_1[i_1 \dots i_2]$  and  $R_2[j_1 \dots j_2]$  such that the alignment ends with  $R_2[j_2]$  aligned to  $'-'$ .

In the lemmas that follow, we attach an index to  $A$ ,  $D$  and  $I$  to indicate the phase of execution.

As most of the lemmas are proved in [12], we give the proofs pertaining to the modified lemmas with respect to those therein.

### 5.1.1 Phase 1

**Lemma 5.1** [12]

$$A_1(\emptyset, \emptyset) = 0, \quad D_1(\emptyset, \emptyset) = -g, \quad I_1(\emptyset, \emptyset) = -g.$$

*Proof.* For  $A_1(\emptyset, \emptyset)$ , consider  $A_1(i_1, j_1)$  when the optimal alignment results from aligning  $R_1[i_1]$  to  $R_2[j_1]$ , in which case  $A_1(i_1, j_1) = \gamma(i_1, j_1)$ . In comparison with the first case in lemma 5.5, we may set  $A_1(\emptyset, \emptyset) = 0$ .

For  $D_1(\emptyset, \emptyset)$ , consider  $D_1(i_1, \emptyset)$  by which  $R_1[i_1]$  is aligned to  $'-'$  and a gap is opened, hence  $D_1(\emptyset, \emptyset) = -g$ .

Similarly, we may obtain that  $I_1(\emptyset, \emptyset) = -g$ . Moreover, if we substitute the values of  $A_1(\emptyset, \emptyset)$  and  $D_1(\emptyset, \emptyset)$  into lemma 5.3 considering  $D_1(i_1, \emptyset)$ , we have the same value for both possibilities. This is true since there is only one way to align  $R_1[i_1]$  to  $'-'$ , hence only one possible value to select.  $\square$

**Lemma 5.2** [12] For  $i_1 \leq i \leq i_2$  and  $j_1 \leq j \leq j_2$ ,

$$\begin{aligned} D_1(i_1 \dots i, \emptyset) &= D_1(i_1 \dots i-1, \emptyset) - \delta(i, 0), \\ A_1(i_1 \dots i, \emptyset) &= D_1(i_1 \dots i, \emptyset), \\ I_1(i_1 \dots i, \emptyset) &= D_1(i_1 \dots i, \emptyset) - g, \\ I_1(\emptyset, j_1 \dots j) &= I_1(\emptyset, j_1 \dots j-1) - \delta(0, j), \\ A_1(\emptyset, j_1 \dots j) &= I_1(\emptyset, j_1 \dots j), \\ D_1(\emptyset, j_1 \dots j) &= I_1(\emptyset, j_1 \dots j) - g. \end{aligned}$$

*Proof.* For  $D_1(i_1 \dots i, \emptyset)$ , by definition  $R_1[i]$  is aligned to  $'-'$ , hence the  $-\delta(i, 0)$  term; and  $R_1[i_1 \dots i-1]$  is aligned to  $\emptyset$ . There is only one possibility, namely, each element in  $R_1[i_1 \dots i-1]$  is aligned to  $'-'$ , by which we know that  $R_1[i-1]$  is also aligned to  $'-'$ , hence by definition the  $D_1(i_1 \dots i-1, \emptyset)$  term.

For  $A_1(i_1 \dots i, \emptyset)$ , this is the optimal alignment between  $R_1[i_1 \dots i]$  and  $\emptyset$ . There is only one possibility, namely, each element in  $R_1[i_1 \dots i]$  is aligned to  $'-'$ , by which we know that  $R_1[i]$  is also aligned to  $'-'$ , hence by definition  $A_1(i_1 \dots i, \emptyset) = D_1(i_1 \dots i, \emptyset)$ .

For  $I_1(i_1 \dots i, \emptyset)$ , consider  $I_1(i_1 \dots i, j_1)$ , the optimal alignment between  $R_1[i_1 \dots i]$  and  $R_2[j_1]$  that ends with  $R_2[j_1]$  aligned to  $'-'$ . This yields only one possible alignment, namely,  $R_2[j_1]$  is aligned to  $'-'$  and each element in  $R_1[i_1 \dots i-1]$  is aligned to  $'-'$ . Therefore, both possibilities in lemma 5.4 should yield the same value for  $I_1(i_1 \dots i, j_1)$ . That is,  $I_1(i_1 \dots i, \emptyset) - \delta(0, j) = A_1(i_1 \dots i, \emptyset) - \delta(0, j) - g$ . We have just shown that  $A_1(i_1 \dots i, \emptyset) = D_1(i_1 \dots i, \emptyset)$ , hence  $I_1(i_1 \dots i, \emptyset) = D_1(i_1 \dots i, \emptyset) - g$ . Meanwhile, we may think that aligning  $R_2[j_1]$  to  $'-'$  opens a gap, hence the  $-g$  term. Then there is only one way to optimally align  $R_1[i_1 \dots i]$  to  $\emptyset$ , namely, aligning each element in  $R_1[i_1 \dots i]$  to  $'-'$ , which forces  $R_1[i]$  to be aligned to  $'-'$ , hence the  $D_1(i_1 \dots i, \emptyset)$  term. If  $I_1(i_1 \dots i, j_1)$  comes from  $I_1(i_1 \dots i, \emptyset)$ , then  $I_1(i_1 \dots i, \emptyset)$  must account for both terms. Applying same line of arguments for  $D_1(i_1 \dots i, \emptyset)$ ,  $A_1(i_1 \dots i, \emptyset)$  and  $I_1(i_1 \dots i, \emptyset)$  yields the corresponding formulae for  $I_1(\emptyset, j_1 \dots j)$ ,  $A_1(\emptyset, j_1 \dots j)$  and  $D_1(\emptyset, j_1 \dots j)$ , respectively.  $\square$

**Lemma 5.3** [12] For  $i_1 \leq i \leq i_2$  and  $j_1 \leq j \leq j_2$ ,

$$\begin{aligned} D_1(i_1 \dots i, j_1 \dots j) \\ = \max \begin{cases} D_1(i_1 \dots i-1, j_1 \dots j) - \delta(i, 0), \\ A_1(i_1 \dots i-1, j_1 \dots j) - \delta(i, 0) - g. \end{cases} \end{aligned}$$

**Lemma 5.4** [12] For  $i_1 \leq i \leq i_2$  and  $j_1 \leq j \leq j_2$ ,

$$I_1(i_1 \dots i, j_1 \dots j)$$

$$= \max \begin{cases} I_1(i_1 \dots i, j_1 \dots j-1) - \delta(0, j), \\ A_1(i_1 \dots i, j_1 \dots j-1) - \delta(0, j) - g. \end{cases}$$

**Lemma 5.5** [12] For  $i_1 \leq i \leq i_2$  and  $j_1 \leq j \leq j_2$ , if  $i = p(R_1[i])$  and  $j = p(R_2[j])$ , then

$$A_1(i_1 \dots i, j_1 \dots j) = \max \begin{cases} D_1(i_1 \dots i, j_1 \dots j), \\ I_1(i_1 \dots i, j_1 \dots j), \\ A_1(i_1 \dots i-1, j_1 \dots j-1) + \gamma(i, j); \end{cases}$$

if  $i_1 \leq p(R_1[i]) < i$  and  $j_1 \leq p(R_2[j]) < j$ , then

$$A_1(i_1 \dots i, j_1 \dots j) = \max \begin{cases} D_1(i_1 \dots i, j_1 \dots j), \\ I_1(i_1 \dots i, j_1 \dots j), \\ A_1(i_1 \dots p(R_1[i])-1, j_1 \dots p(R_2[j])-1) \\ + A_1(p(R_1[i]) + 1 \dots i-1, p(R_2[j]) + 1 \dots j-1) \\ + \gamma(i, j); \end{cases}$$

otherwise,

$$A_1(i_1 \dots i, j_1 \dots j) = \max \begin{cases} D_1(i_1 \dots i, j_1 \dots j), \\ I_1(i_1 \dots i, j_1 \dots j). \end{cases}$$

### 5.1.2 Phase 2

The lemmas in phase 1 are for global alignment. For our interested problem, namely finding the best fit of  $R_1$  in  $R_2$ , we need to modify some of those lemmas.

The major changes occur in the boundary conditions, i.e., lemmas 5.6 and 5.7. The idea for the boundary conditions is the same as that in the sequence case [13]. That is, initial alignments to  $'-'$  in  $R_2$  are not accounted for as penalties until the first match is met; each alignment to  $'-'$  thereafter in  $R_2$  accounts for a penalty. For  $R_1$ , however, each alignment to  $'-'$  accounts for a penalty.

Additionally in case 2 of lemma 5.10, an  $A_1$  term is used because it corresponds to an alignment between two substructures, each delimited by a base pair, that has been computed in phase 1.

Other than the above-mentioned changes, the lemmas in phase 2 are the same as those in phase 1.

#### Lemma 5.6

$$A_2(\emptyset, \emptyset) = 0, \quad D_2(\emptyset, \emptyset) = -g.$$

*Proof.* Since this is a subset of lemma 5.1, same arguments hold.  $\square$

**Lemma 5.7** For  $1 \leq i \leq |R_1|$  and  $1 \leq j \leq |R_2|$ ,

$$\begin{aligned} D_2(1 \dots i, \emptyset) &= D_2(1 \dots i-1, \emptyset) - \delta(i, 0), \\ A_2(1 \dots i, \emptyset) &= D_2(1 \dots i, \emptyset), \\ I_2(1 \dots i, \emptyset) &= D_2(1 \dots i, \emptyset) - g, \\ A_2(\emptyset, 1 \dots j) &= 0, \\ D_2(\emptyset, 1 \dots j) &= -g. \end{aligned}$$

*Proof.* We prove only the modified part with respect to lemma 5.2.

For  $A_2(\emptyset, 1 \dots j)$ , the only possibility is to align each element in  $R_2(1 \dots j)$  to  $'-'$ . In finding the best fit of a pattern in  $R_2$ , each initial alignment to  $'-'$  in  $R_2$  before the first match is not accounted for as penalty, hence  $A_2(\emptyset, 1 \dots j) = 0$ .

For  $D_2(\emptyset, 1 \dots j)$ , consider  $D_2(1, 1 \dots j)$  when  $R_1[1]$  is aligned to  $'-'$ , which means that a gap is opened, hence  $D_2(\emptyset, 1 \dots j)$  accounts for the  $-g$  term. Consequently, the entire  $R_2[1 \dots j]$  can only be aligned to  $'-'$ . As just mentioned, this does not invoke a penalty, hence no other terms are accounted for by  $D_2(\emptyset, 1 \dots j)$ .  $\square$

**Lemma 5.8** [12] For  $1 \leq i \leq |R_1|$  and  $1 \leq j \leq |R_2|$ ,

$$D_2(1 \dots i, 1 \dots j) = \max \begin{cases} D_2(1 \dots i-1, 1 \dots j) - \delta(i, 0), \\ A_2(1 \dots i-1, 1 \dots j) - \delta(i, 0) - g. \end{cases}$$

**Lemma 5.9** [12] For  $1 \leq i \leq |R_1|$  and  $1 \leq j \leq |R_2|$ ,

$$I_2(1 \dots i, 1 \dots j) = \max \begin{cases} I_2(1 \dots i, 1 \dots j-1) - \delta(0, j), \\ A_2(1 \dots i, 1 \dots j-1) - \delta(0, j) - g. \end{cases}$$

**Lemma 5.10** [12] For  $1 \leq i \leq |R_1|$  and  $1 \leq j \leq |R_2|$ , if  $i = p(R_1[i])$  and  $j = p(R_2[j])$ , then

$$A_2(1 \dots i, 1 \dots j) = \max \begin{cases} D_2(1 \dots i, 1 \dots j), \\ I_2(1 \dots i, 1 \dots j), \\ A_2(1 \dots i-1, 1 \dots j-1) + \gamma(i, j); \end{cases}$$

if  $1 \leq p(R_1[i]) < i$  and  $1 \leq p(R_2[j]) < j$ , then

$$A_2(1 \dots i, 1 \dots j) = \max \begin{cases} D_2(1 \dots i, 1 \dots j), \\ I_2(1 \dots i, 1 \dots j), \\ A_2(1 \dots p(R_1[i])-1, 1 \dots p(R_2[j])-1) \\ + A_1(p(R_1[i]) + 1 \dots i-1, p(R_2[j]) + 1 \dots j-1) \\ + \gamma(i, j); \end{cases}$$

otherwise,

$$A_2(1 \dots i, 1 \dots j) = \max \begin{cases} D_2(1 \dots i, 1 \dots j), \\ I_2(1 \dots i, 1 \dots j). \end{cases}$$

## 5.2 Algorithm

We use a bottom-up dynamic-programming algorithm executing two phases described as follows.

### 5.2.1 Phase 1

In this phase, we compute alignments between substructures as follows. We compute the alignments between every pair of substructures  $R_1[i_1 + 1 \dots i_2 - 1]$  and  $R_2[j_1 + 1 \dots j_2 - 1]$ , where  $p(R_1[i_1]) = i_2$  and  $p(R_2[j_1]) = j_2$  (i.e.,  $i_1$  and  $i_2$  form a base pair in  $R_1$ ; ditto for  $j_1$  and  $j_2$  in  $R_2$ ). For nested pairs, we start with the innermost pair then proceed outwards.

Specifically, given  $R_1$  and  $R_2$ , we first sort  $P(R_1)$  and  $P(R_2)$  by 3' end into two sorted lists  $L_1$  and  $L_2$ , respectively. For each pair of base pairs  $(L_1[i], L_2[j])$ , where  $L_1[i] = (i_1, i_2)$  and  $L_2[j] = (j_1, j_2)$ , we use lemmas 5.1 to 5.5 to compute  $A_1(i_1 + 1 \cdots i_2 - 1, j_1 + 1 \cdots j_2 - 1)$ .

### 5.2.2 Phase 2

In this phase, we take the two whole structures,  $R_1$  and  $R_2$ , and compute  $A_2(R_1, R_2) = A_2(1 \cdots |R_1|, 1 \cdots |R_2|)$  using lemmas 5.6 to 5.10.

### 5.2.3 Finding the Best Fit

To find the best fit involving  $R_1[1 \cdots m]$  and  $R_2[k \cdots l]$ , where  $m = |R_1|$ , we can do a traceback starting at  $A_{2m,l}(R_1, R_2)$ , where the subscript  $(m, l)$  refers to the entry position in the associated matrix. Note that traceback may involve multiple matrices.

### 5.2.4 Complexities

The running time to compute  $A_i(i_1 \cdots i_2, j_1 \cdots j_2)$ ,  $D_i(i_1 \cdots i_2, j_1 \cdots j_2)$  and  $I_i(i_1 \cdots i_2, j_1 \cdots j_2)$ , where  $i = 1$  or  $2$ , is bounded by  $O(|R_1||R_2|)$ . Let  $P_1$  and  $P_2$  be the numbers of base pairs in  $R_1$  and  $R_2$ , respectively. The worst-case time complexity of the algorithm is  $O(P_1 P_2 |R_1| |R_2|)$ , which can be improved to  $O(S_1 S_2 |R_1| |R_2|)$  where  $S_1$  and  $S_2$  are the numbers of stems in  $R_1$  and  $R_2$ , respectively. The space complexity of the algorithm is  $O(|R_1| |R_2|)$ .

## 6 Local Alignment

In this section, we consider the local structural alignment problem. The ideas follow directly from the sequence case [13]. With respect to the structural case, it is a simple extension from the approximate structural pattern matching problem in section 5. We also use a two-phase procedure much the same as presented in section 5. The lemmas for phase 1 are the same as those in phase 1 of section 5. We list only the lemmas for phase 2. The modifications are trivial. Same proof reasonings in section 5 can easily apply here. Due to page limit, we omit the proofs. We remark two major changes. First, the boundary conditions. Essentially, if we extend half of the boundary conditions of the approximate pattern matching problem to the other half, we get the boundary conditions for the local alignment problem. This is easy to see since the boundary conditions for the text structure behave just like local alignment. Secondly, in computing the optimal-alignment score, an additional possibility is included, namely 0.

#### Lemma 6.1

$$A_2(\emptyset, \emptyset) = 0.$$

$$\begin{aligned} \text{Lemma 6.2} \quad & \text{For } 1 \leq i \leq |R_1| \text{ and } 1 \leq j \leq |R_2|, \\ & A_2(1 \cdots i, \emptyset) = 0, \quad I_2(1 \cdots i, \emptyset) = -g, \\ & A_2(\emptyset, 1 \cdots j) = 0, \quad D_2(\emptyset, 1 \cdots j) = -g. \end{aligned}$$

$$\text{Lemma 6.3} \quad \text{For } 1 \leq i \leq |R_1| \text{ and } 1 \leq j \leq |R_2|,$$

$$D_2(1 \cdots i, 1 \cdots j)$$

$$= \max \begin{cases} 0, \\ D_2(1 \cdots i - 1, 1 \cdots j) - \delta(i, 0), \\ A_2(1 \cdots i - 1, 1 \cdots j) - \delta(i, 0) - g. \end{cases}$$

$$\text{Lemma 6.4} \quad \text{For } 1 \leq i \leq |R_1| \text{ and } 1 \leq j \leq |R_2|,$$

$$I_2(1 \cdots i, 1 \cdots j)$$

$$= \max \begin{cases} 0, \\ I_2(1 \cdots i, 1 \cdots j - 1) - \delta(0, j), \\ A_2(1 \cdots i, 1 \cdots j - 1) - \delta(0, j) - g. \end{cases}$$

$$\text{Lemma 6.5} \quad \text{For } 1 \leq i \leq |R_1| \text{ and } 1 \leq j \leq |R_2|,$$

$$\text{if } i = p(R_1[i]) \text{ and } j = p(R_2[j]), \text{ then}$$

$$A_2(1 \cdots i, 1 \cdots j)$$

$$= \max \begin{cases} 0, \\ D_2(1 \cdots i, 1 \cdots j), \\ I_2(1 \cdots i, 1 \cdots j), \\ A_2(1 \cdots i - 1, 1 \cdots j - 1) + \gamma(i, j); \end{cases}$$

$$\text{if } 1 \leq p(R_1[i]) < i \text{ and } 1 \leq p(R_2[j]) < j, \text{ then}$$

$$A_2(1 \cdots i, 1 \cdots j) = \max$$

$$\begin{cases} 0, \\ D_2(1 \cdots i, 1 \cdots j), \\ I_2(1 \cdots i, 1 \cdots j), \\ A_2(1 \cdots p(R_1[i]) - 1, 1 \cdots p(R_2[j]) - 1) \\ + A_1(p(R_1[i]) + 1 \cdots i - 1, p(R_2[j]) + 1 \cdots j - 1) \\ + \gamma(i, j); \end{cases}$$

$$\text{otherwise,}$$

$$A_2(1 \cdots i, 1 \cdots j) = \max \begin{cases} 0, \\ D_2(1 \cdots i, 1 \cdots j), \\ I_2(1 \cdots i, 1 \cdots j). \end{cases}$$

## 7 Conclusions

We have presented three algorithms, of which, two pertain to the exact and approximate RNA structural pattern matching problems; and one, the local RNA structural alignment problem.

In the exact pattern-matching algorithm, we use a labelling device to preserve the relative structural information within a given RNA structure, thereby facilitating direct use of an existing fast string-matching algorithm on the exact RNA structural pattern matching problem.

In the approximate pattern-matching algorithm, we adapt an earlier work in RNA structural alignment to the approximate RNA structural pattern matching problem.

We further extend the approximate pattern-matching algorithm to adapt to the local RNA structural alignment problem.

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